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DISTRIBUTION OF "MODEL" CONGENITAL MALFORMATIONS IN CHILDREN WHOSE MOTHERS USED TO LIVE IN THE ENVIRONMENTALLY UNFAVOURABLE AREAS

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Abstract

To determine the frequency of "model" congenital malformations in children whose mothers used to live in places with different geochemical characteristics in Chernivtsi and to define the risk indices of their formation.

Material and methods. Retrospective analysis was carried out on 117 protocols of dissections of newborns and fetuses with CM, who died in utero or after birth in 2004-2014 in Chernivtsi and 489 genetic records of children born in Chernivtsi with "model" birth defects were also analyzed.

Results. A ten-year analysis showed that the frequency of "model" CM in Chernivtsi in general corresponds to the EUROCAT International Register indices, with the exception of

multiple birth defects, which exceeded the European index by 2.4 times, hypospadias – by 6 times, and congenital hydrocephalus , the index of which was on the upper limit.

Conclusions. A significant risk of the formation of birth defects of the heart, the central nervous system and the genitourinary system was detected in the structure of "model" congenital malformations, provided that the mothers lived in places of geochemical disadvantages. The mortality of males with congenital malformations was higher than that of female children.

Key words: **heavy metals, pollution, developmental defects, newborns.**

Congenital malformations (CM) constitute a significant part in the structure of the causes of morbidity, infant mortality and disability. Most CM have multifactorial etiology, which means the simultaneous influence of genetic predisposition and external stimuli [2, 3]. Many authors suggest using CM as an indicator of mutagenic and teratogenic effects, especially within territories with a high level of environmental load [4, 6]. Among all the CM, the so-called "model" CM which are recommended for mandatory registration in the EUROCAT register [1], are markedly less frequent. These defects of development are used to determine the interaction of genetic and environmental contamination factors in the occurrence of congenital anomalies [5]. The absence of information on the frequency and the structure of the "model" CM, depending on the areas of environmental disadvantage, confirms the need for research in this direction, the results of which will permit to determine the risks of congenital malformations.

The objective of the work. To determine the frequency of "model" congenital malformations in children whose mothers used to live in places with different geochemical characteristics in Chernivtsi and to define the risk indices of their formation.

Material and methods. Retrospective analysis was carried out on 117 protocols of dissections of newborns and fetuses with CM, who died in utero or after birth in 2004-2014 in Chernivtsi. The dissections were performed at the municipal health care facility "Pathologist's Office" (head – Hrechko D.I.) in Chernivtsi. The analysis included cases of perinatal, neonatal losses caused by CM. 489 genetic records of children born in Chernivtsi with "model" birth defects were also analyzed. All of their forms, detected in newborns, stillborn and dead children, as well as in aborted fetuses during the mentioned period of time, were recorded to estimate the general frequency of CM.

The population frequency of CM was calculated according to the EUROCAT formula, as the ratio of the number of live births and stillbirths (including abortion fetuses) with birth defects to the total number of live births and stillborns in Chernivtsi multiplied by 1.000 [7]: General frequency of CM = Number of CM cases (LB+FD+IA)/Birth rate index (LB+FD) x 1000, where LB – live births; FD – stillborn; IA – the fetuses of abortions with CM weighing 500 grams and aged 22 or more weeks of gestational period; CM frequency is calculated per 1000 births.

Geochemical disadvantages of the places of mothers' residence, whose children were born with "model" birth defects, were determined based on the results of soils study in Chernivtsi, carried out by the geological association "Pivnichukrgeologiya" (1993) and Yu. Fedkovych Chernivtsi National University (1992). The content of heavy metals in the soil was estimated by the integral coefficient of contamination, calculated as the sum of the ratio of the content of certain heavy metals to the maximum permissible concentration. The results allowed to mark the places of living of mothers, whose children died, as "contaminated with heavy metals" (CHM), as well as conditionally "clean" (CC). The values that went beyond +2 σ from the mean were considered as the point of differentiation.

Two groups of observations were created, depending on the geochemical disadvantages of the places of residence of the mothers of children born with "model" birth defects. The first (I) group involved 327 cases, which belonged to the CHM according to the place of residence. And the second (II) group included 162 cases in the families, referred to CC by the place of residence.

The obtained data were analyzed by means of the methods of biostatistics using the principles of clinical epidemiology, with the help of the computer programs "STATISTICA" StatSoft Inc. and Excel XP for Windows on a personal computer using parametric and nonparametric computing methods [8]. The risk of CM in children was estimated by the ratio of chances (RC) to the relative risk (RR) determining a 95% confidence interval (95%CI), as well as by the magnitude of attributional risk (AR) [9].

Results of the research and their discussion

During 2004-2014 there were 30304 deliveries in Chernivtsi, 30076 of which finished with live births and 228 were stillborn. To analyze the data, we used a group of birth defects of mandatory record. This group included 18 birth defects (spinal hernia, encephalocele, congenital hydrocephalus, congenital heart defects: transposition of large vessels, hypoplasia of the left portions of the heart, cleft palate, cleft upper lip, cleft palate and upper lip, esophageal atresia,

atresia of the anus, hypospadias , diaphragmatic hernia, multiple congenital malformations (MCM) and Down's syndrome).

To determine the structure of CM, all registered defects were divided according to the International Classification of Diseases-10 (ICD-10) into groups:

- congenital malformations of the nervous system (Q00-Q07)
- congenital malformations of the eyes, ears, face and eyes (Q10-Q18)
- congenital malformations of the circulatory system (Q20-Q28)
- congenital malformations of the respiratory organs (Q30-Q34)
- congenital malformations of the gastrointestinal tract (Q35-Q45)
- congenital malformations of the reproductive system (Q50-Q56)
- congenital malformations of the urinary tract (Q60-Q64)
- congenital malformations of the musculoskeletal system (Q65-Q79)
- congenital anomalies of the skin and appendages (Q80-Q85)
- other congenital anomalies, including multiple birth defects (Q86-Q89)
- chromosomal disorders (Q90-Q99)

Table 1 demonstrates the comparative characteristics of CM of the mandatory registration among newborns and fetuses in Chernivtsi and EUROCAT.

Therefore, the prevalence of CM subject to mandatory registration in Chernivtsi corresponds to the EUROCAT International Registry rates, with the exception of MCM, hypospadias, which exceeded this index, and cases of congenital hydrocephalus, which were at the upper limit of the index. According to EUROCAT and some authors [1, 2, 4], this may indicate an environmental disadvantage in the city.

It has been established that in the structure of "model" congenital malformations in Chernivtsi, MCM (35%) and congenital malformations of the heart (18%) are the most frequent, birth defects of the reproductive system and Down's syndrome stand third – 11% each. The malformations of the musculoskeletal system and the central nervous system were detected in 7% of cases, facial and neck-defects – in 6% of cases. The birth defects of the urinary system and the gastrointestinal tract occur in 2%, respiratory organs – in 1% of cases.

Table 2 shows the distribution of the prevalence of "model" defects in children of clinical comparison groups formed depending on the geochemical characteristics of places of living of their mothers.

Table 1

Comparative characteristics of congenital malformations of the mandatory registration in Chernivtsi and EUROCAT (per 1000 newborns)

№	Congenital malformations of the mandatory registration (ICD 10)	Chernivtsi	EUROCAT
1	Congenital hydrocephalus	**0.80**	0.20-0.80
2	Spinal and cerebral hernia	0.40	0.10-0.70
3	Congenital heart defects Including:	3.0	5.0-7.0
-	Transposition of large vessels	0.40	0.10-0.61
-	Hypoplasia of the left portions of the heart	0.16	0.00-0.35
6	Cleft palate	0.30	0.2-0.8
7	Cleft upper lip	0.40	0.4-0.9
8	Cleft palate and upper lip	0.16	0.6-1.7
9	Esophageal atresia	0.19	0.10-0.50
10	Atresia of the anus	0.13	0.10-0.50
11	Hypospadias	**1.60**	0.1-0.26
12	Agenesis and dysgenesis of the kidneys	0.33	0.02-0.40
13	Polydactylism	1.0	0.4-1.18
14	Diaphragmatic hernia	0.32	0.03-0.40
15	MCM	**5.70**	0.90-2.40
16	Down's syndrome	1.81	0.70-1.40

Table 2

Distribution of the frequency of congenital malformations of certain organ systems depending on the geochemical characteristics of places of living

Geochemical characteristics of places of living	Number of children with "model" CM	Distribution of "model" congenital malformations in the structure (abs/%)							
		Multiple congenital malformations	Down's syndrome	Cardio-vascular system	Urinary system	Musculoskeletal system	Gastrointestinal tract	Central nervous system	Facial defects
CHM	327	106/32.4	36/11.0	66/20.1	46/14.0	24/7.3	6/1.8	26/8.0	17/5.2
CC	162	67/41.3	19/11.7	22/13.5	15/9.2	11/6.8	4/2.5	8/4.9	10/6.2
P		< 0.05	> 0.05	< 0.05	< 0.05	> 0.05	> 0.05	<0.05	> 0.05

Note: *CHM – contaminated with heavy metals, **CC – soil is conditionally "clean"

Thus, the given data make it possible to assume that in places of ecological disadvantages congenital heart defects predominated in compared to the II group, which is relatively favorable by the geochemical characteristics of the habitats. It should be noted that the relative risk of development of congenital heart defects in group I in relation to the comparison group was RR=1.5 (95CI 1.3-1.7) attributive risk – 0.07. In spite of a significant proportion of cases of MCM in children in the general sample, while dividing into the comparison groups with an alternative characteristic of contamination by heavy metals, more cases were found in conditionally pure zones RR=0.78 (95CI 0.68-0.9), which indicates a multifactorial effect of other unrecognized factors on their formation. The risk of development of birth defects of the central nervous system on the territories identified as unfavorable due to the ecological characteristics of the soils is 1.66 (95CI 1.36-2.0), the attributive risk is 0.03, and the urogenital malformations – 1.53 (95CI 1.3-1.8) and 0.05 respectively.

In both groups, birth defects predominated in fetuses and newborn males, but the prevalence of such cases occurred in areas with unfavorable soil characteristics.

So, in the I group, the frequency of CM in fetuses and male infants reached 71.0±2.5% of cases, whereas in the II group it was 60.4±3.84% ($p<0.05$).

The relative risk of birth defects development in male representatives whose mothers lived in areas of soil contamination by heavy metals was 1.27 (95CI 1.04-1.6).

It was found that 46 children (14.0% of cases) died in group I and 16 (9.8% of cases) – in group II. Among the deceased children, males were dominated in both groups – 12.9% in the first group and 6.7% in the second group. Fatal cases among female representatives were 1.1% and 3.1% respectively ($p<0.05$).

Thus, a ten-year analysis showed that the frequency of “model” CM in Chernivtsi in general corresponds to the EUROCAT International Register indices, with the exception of multiple birth defects, which exceeded the European index by 2.4 times, hypospadias – by 6 times, and congenital hydrocephalus , the index of which was on the upper limit. A significant risk of the formation of birth defects of the heart, the central nervous system and the genitourinary system was detected in the structure of “model” congenital malformations, provided that the mothers lived in places of geochemical disadvantages. The mortality of males with congenital malformations was higher than that of female children.

Conclusions

1. In Chernivtsi multiple birth defects (index – 5.70) and hypospadias (index – 1.60) exceed those of the International Register EUROCAT. The incidence of congenital hydrocephalus corresponds to the upper limit of the EUROCAT index and constitutes 0.8.

2. Under the condition of mothers' living in ecologically unfavorable areas of the city, the risk of birth defects of the heart is increased RR=1.5, the central nervous system – 1.66 and the urogenital system – 1.53 in newborn babies.

3. The prevalence of multiple birth defects of the heart is slightly prevalent in the conditionally clean areas of the city RR=0.78.

4. Congenital malformations of mandatory record regardless of the ecological characteristics of habitats develop more often in boys: in group I in 71.0%, in group II in 60.4%. Fatal cases were more likely to be observed in males than in females.

Prospects for further research. To investigate the influence of air pollution on the occurrence of birth defects in newborn babies.

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